PATENT SPECIFICATION

(11) 1 533 529

1 533 529

(21) Application No. 6704/77 (22) Filed 17 Feb. 1977
(31) Convention Application Nos. 658 961 and 658 979
(32) Filed 18 Feb. 1976 in
(33) United States of America (US)
(44) Complete Specification published 29 Nov. 1978
(51) INT CL² C07D 413/14; A61K 31/505; C07D 417/14; (C07D 413/14, 261/18, 263/34, 271/10, 295/16) (C07D 417/14, 239/94, 275/02, 277/56)
(52) Index at acceptance
C2C 1370 1371 1380 1382 1432 1604 1626 213 215 247 250 252 255 256 25Y 28X 29X 29Y 30Y 321 32Y 351 355 35X 364 36Y 373 37Y 614 620 625 634 670 672 675 790 79Y LM RM

(72) Inventors RICHARD ANTHONY PARTYKA and RONNIE RAY CRENSHAW

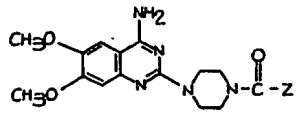
(19)

(54) 4-AMINO-6,7-DIMETHOXY-2-[4-(HETEROCYCLOCARBONYL) PIPERAZIN-1-YL] QUINAZOLINES

(71) We, BRISTOL-MYERS COMPANY, a Corporation organised and existing under the laws of the State of Delaware, United States of America, having offices located at 345 Park Avenue, New York, New York 10022, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

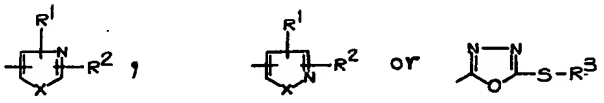
This invention relates to nitrogen containing heterocyclic carbonyl piperazinyl quinazolines which are potent antihypertensive drugs having generally less α-adrenergic blocking activity than does 2-[4-(2-furoyl)piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline which is a known potent antihypertensive drug.

More particularly, this invention relates to compounds having the formula



I

wherein Z is



wherein X is either oxygen or sulfur, R^1 and R^2 may be the same or different and are selected from hydrogen, alkyl having from 1 to 6 carbon atoms, alkoxy having from 1 to 6 carbon atoms and alkylthio having from 1 to 6 carbon atoms, and R^3 is alkyl having from 1 to 6 carbon atoms; or pharmaceutically acceptable acid addition salts thereof.

The invention also includes processes for the preparation thereof.

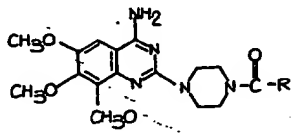
United States Patent Nos. 3,511,386; 3,635,979 and 3,663,706 disclose several 4 - amino - 6,7 - dimethoxy - 2 - [4 - (heterocyclic - 2 - carbonyl) - piperazin - 1-yl] quinazolines. One of these compounds, i.e. 2-[4-(2-furoyl)-piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline described in Example LXXII of these Patents is a clinically useful antihypertensive agent and is marketed as such in many countries of the world under the generic name prazosin. It is well established that the antihypertensive efficacy of prazosin results from a dual mechanism f action:

(i) a direct peripheral vasodilatation effect on vascular smooth muscle; and,
(ii) a functional peripheral α-adrenergic receptor blockade,

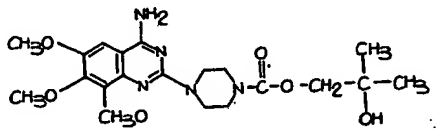
H. Adriaensen, *The Practitioner, 214,* 268 (1975);
Mroczek, et al., *Current Therapeutic Research, 16,* 769 (1974);
Scriabine, et al., *Experientia, 24,* 1150 (1968);
Constantine, et al., "Hypertension: Mechanisms and Management", ed. by Onesti, Kim and Moyer;
Grune and Stratton, 1973 pp. 429—44; and
Zacest, *Med. J. of Austral. Special Supplement, 1,* 4 (1975).

Although initial clinical assessments on prazosin indicated an almost complete absence of side effects, recent reports have revealed severe adverse reactions of postural hypotension in some patents, Bendall, et al., *Brit. Med. J.,* 727 (June 28, 1975); Rees, *Brit. Med. J.,* 593 (Sept. 6, 1975); Gabriel, et al., *The Lancet,* 1095 (May 10, 1975); and, Bloom, et al., *Current Therapeutic Research, 18,* 144 (1975). It is generally felt that this type of side effect results from the α-blockade component of prazosin. Indeed, it has been stated by R. Zacest in the *Med. J. of Austral., Special Supplement, 1,* 4 (1975) that "if the alpha adrenergic 'blocking' activity does prove to be significant with high doses it may lead to postural hypotension".

United States Patents Nos. 3,669,968 and 3,769,286 cover trialkoxyquinazolines, such as those having the formula:

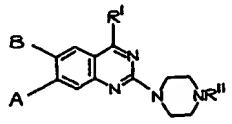


wherein R may be a number of different groups including furyl and thienyl. These patents claim to have certain advantages over the corresponding 6,7-dialkoxy compounds such as those disclosed in the patents previously discussed. Thus, it is stated that such compounds "have a more favourable pharmacological profile (e.g., they are non-adrenolytic in dogs) and possess greatly improved solubility characteristics (particularly in water) as contrasted to the corresponding 6,7-dialkoxy compounds reported in the prior art". One of the compounds disclosed in these patents is known by the generic name trimazosin and has the formula:



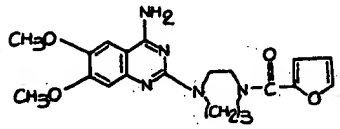
Trimazosin is reported to be active in humans as an antihypertensive agent, DeGuia, et al., *Current Therapeutic Research, 15,* 339 (1973); Vlachakis, et al., *Current Therapeutic Research, 17,* 564 (1975). However, it is a much weaker drug than prazosin, the respective clinical daily dose ranges being approximately 150 to 500 mg. for trimazosin as compared to 1.5 to 15 mg. for prazosin. Trimazosin is therefore 100-fold weaker than prazosin at the lower end of the dosage range.

U.S. Patent Nos. 3,517,005; 3,594,480; and 3,812,127 describe certain piperazinyl quinazolines having both broncho-dilator and antihypertensive activity, e.g., a compound having the formula:

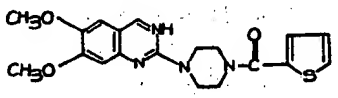


wherein A and B may each be alkoxy, etc., R′ may be hydrogen or alkyl and R″ may be hydrogen or a radical such as alkyl, benzoyl, etc.

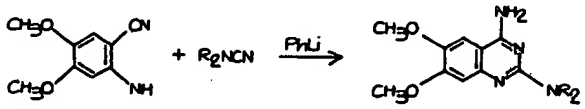
U.S. Patent No. 3,920,636 describes homopiperazino quinazolines as antihypertensive agents, e.g., the compound:



U.S. Patent No. 3,780,040 discloses compounds useful as antihypertensive agents such as the compound:

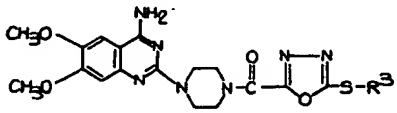


Netherlands Application 72 06,06 (*CA*, *78*, 72180s) describes a process for preparing aminoquinazolines, such as prazosin, by treating the corresponding o-aminobenzonitrile in the presence of phenyl lithium according to the following mechanism:



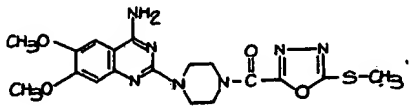
wherein R_2N may be the group 4-(2-furoyl)-1-piperazinyl.

We have found that compounds having the formula I above and pharmaceutically acceptable acid addition salts thereof, possess antihypertensive potency comparable to prazosin but have generally less of the peripheral α-adrenergic blocking properties shown by prazosin. Preferred embodiments of this invention are compounds having the formula:



in which R^3 is (lower)alkyl having from 1 to 4 carbon atoms and pharmaceutically acceptable acid addition salts thereof. These compounds possess antihypertensive potency comparable to prazosin but have little or none of the peripheral α-adrenergic blocking properties shown by prazosin. These compounds are potent antihypertensive agents which have little or no potential for side effects as reflected by their lack of adrenolytic activity.

The most preferred compound of this invention is 4-amino-6,7-dimethoxy-2-[4-(5 - methylthio - 1,3,4 - oxidiazole - 2 - carbonyl)piperazin - 1 - yl] - quinazoline having the formula:



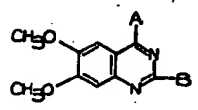
and acid addition salts thereof, in particular, the hydrochloride salt. Other preferred compounds are disclosed hereinafter in the examples, two of which are prepared in the form of the monohydrate thereof.

The term "pharmaceutically acceptable" used herein to describe an acid addition salt of a compound of Formula I refers to those salts of relatively non-toxic inorganic or organic acids. The anion does not contribute appreciably to the toxicity of the salt or to its pharmacological activity. Illustrative of such salts are those formed with acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic acids such as methane-sulfonic, benzenesulfonic and *p*-toluenesulfonic acids. Preparation of the mono-acid addition salts may be carried out in conventional manner by treating a solution or suspension of the free base in a reaction inert organic solvent with one chemical equivalent of the acid or, if the di-acid addition salt is desired, at

least two chemical equivalents of the acid. Conventional concentration or crystallization techniques are employed in isolating the salts.

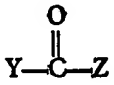
This invention also provides process for the preparation of compounds of the formula I and pharmaceutically acceptable acid addition salts thereof.

According to the present invention, compounds of Formula I are prepared by a process which comprises reacting a quinazoline derivative of Formula II



II

in which substituent A is NH_2 or NR'_2, wherein R'_2 is a conventional amine protecting group, and substituent B is chlorine, piperazino or OR'' wherein R'' is the radical $F_3CC(O)$—, CH_3SO_2—, F_3CSO_2—, or alkyl SO_2— with a reactant selected from

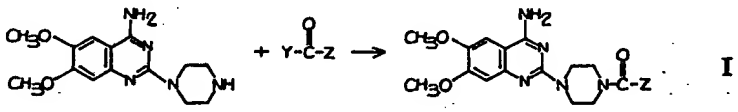


when B is piperazino and

when B is other than piperazino, wherein Y is a carbonyl activating group of the type typically used in amidation reactions, e.g. halo, azido, ethoxy, carbonyloxy and 1-imidazo and Z is as defined above when necessary, removing the amine protecting group R'_2 by conventional means and, if desired, converting the product to a pharmaceutically acceptable acid addition salt by methods known, *per se*.

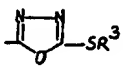
The following reaction schemes of Equations 1—5 illustrate the various synthetic routes embodied in the preparation of the compounds of the present invention according to the process discussed above.

Equation 1.



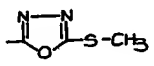
I

In a preferred embodiment of this process, Z is



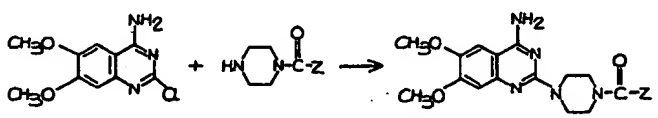
and the reaction is conducted in an inert solvent such as dioxane, chloroform, methylene chloride, or glycol dimethyl ether at room temperature, and/or with heating at reflux to insure completion of the reaction.

In a more preferred embodiment, Y is chlorine, Z is



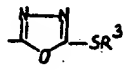
and the reaction is conducted in dioxane.

Equation 2.



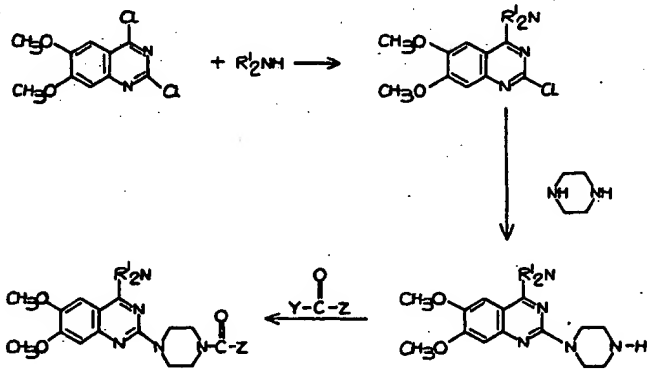
I

In a preferred embodiment of this process, Z is



R^3 being preferably methyl.

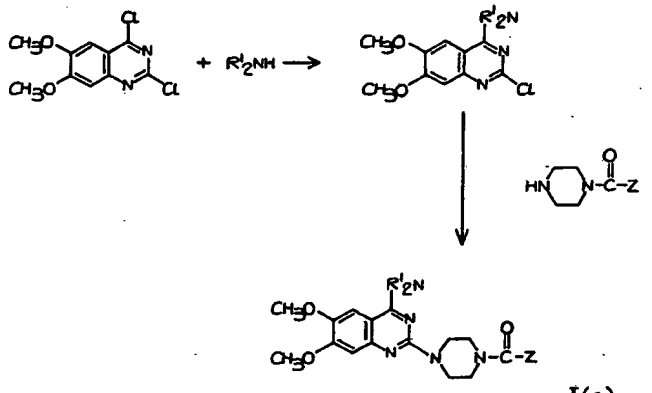
Equation 3.



I(a)

The amine protecting group R'_2 may then be removed from compound I(a) by conventional means to provide the product compound I.

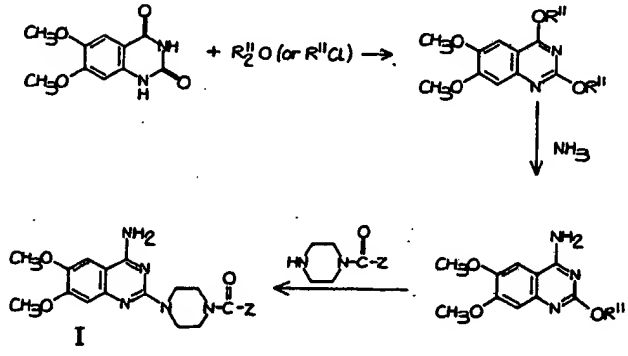
Equation 4.



I(a)

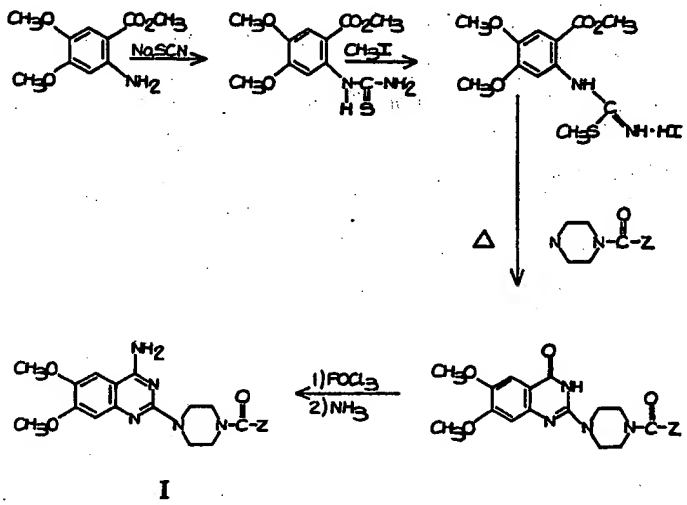
As in the reaction of Equation 3, the amine protecting group R'_2 may be removed from compound Ia by conventional means to provide the product compound I.

Equation 5.



I

The compounds of the present invention may also be prepared by the following reaction sequence:



I

The invention also includes pharmaceutical compositions in dosage unit form adapted for administration to a mammal comprising a compound of the formula I as defined above or a pharmaceutically acceptable acid addition salt thereof. The invention also includes pharmaceutical compositions comprising a compound of formula I as defined above or a pharmaceutically acceptable acid addition salt thereof together with an inert pharmaceutical diluent or carrier.

The following Examples illustrate the invention.

Example 1.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (5 - methylthio - 1,3,4 - oxadiazole - 2-carbonyl) - piperazin - 1 - yl] - quinazoline hydrochloride — A solution of 5-methylthio-1,3,4-oxadiazole-2-carbonyl chloride (0.601 g., 3.36 mmole) in dioxane (10 ml.) was added to a solution of 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline (0.972 g., 3.36 mmole) in dioxane (100 ml.). The resultant mixture was stirred at room temperature for 65 hours, then was heated at reflux for 30 minutes. Filtration gave the title compound (1.56 g.). Recrystallization from methanol gave a product having a M.P. of 280—285°C. with decomposition.

Anal. Calcd for $C_{18}H_{21}N_7O_4S$. HCl: C, 46.20; H, 4.74; Cl, 7.58; N, 20.96; S, 6.85
Found: C, 46.34; H, 4.89; Cl, 7.59; N, 20.38; S, 6.85

Example 2.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (5 - ethylthio - 1,3,4 - oxadiazole - 2-carbonyl) - piperazin - 1 - yl] - quinazoline hydrochloride — The title compound was prepared from 5-ethylthio-1,3,4-oxadiazole-2-carbonyl chloride (0.79 g., 4.1 mmole) and 4-amino-6,7-dimethoxy - 2 - (1 - piperazinyl)quinazoline (1.19 g., 4.1 mmole) following the procedure described in Example 1. The product had a M.P. of 246—248.5°C.

Anal. Calcd for $C_{19}H_{23}N_7O_4S$. HCl: C, 47.34; H, 5.02; N, 20.34; S, 6.65
Found: C, 47.37; H, 4.76; N, 20.15; S, 6.71.
(corrected for 4.11% H_2O)

Example 3.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (5 - isopropylthio - 1,3,4 - oxadiazole - 2-carbonyl) - piperazin - 1 - yl] - quinazoline hydrochloride — The title compound was prepared from 5-isopropylthio-1,3,4-oxadiazole-2-carbonyl chloride (1.54 g., 7.5

mmole) and 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline (2.1 g., 7.5 mmole) following the procedure of Example 1. The product had a M.P. of 260—263°C. with decomposition.

Anal. Calcd for $C_{20}H_{23}N_7O_4S \cdot HCl$: C, 48.43; H, 5.28; N, 19.77
Found: C, 48.05; H, 5.20; N, 19.61.

Example 4.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (5 - n - propylthio - 1,3,4 - oxadiazole - 2 - carbonyl) - piperazin - 1 - yl] - quinazoline hydrochloride — The title compound was prepared from 5-*n*-propylthio-1,3,4-oxadiazole-2-carbonyl chloride (1.68 g., 8.16 mmole) and 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline (2.36 g., 8.16 mmole) following the procedure of Example 1. The product had a M.P. of 230—245°C. with decomposition.

Anal. Calcd for $C_{20}H_{23}N_7O_4S \cdot HCl$: C, 48.43; H, 5.25; N, 19.77
Found: C, 48.11; H, 5.35; N, 19.65.

Example 5.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (5 - n - butylthio - 1,3,4 - oxadiazole - 2 - carbonyl) - piperazine - 1 - yl] - quinazole hydrochloride — The title compound was prepared from 5-*n*-butylthio-1,3,4-oxadiazole-2-carbonyl chloride and 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline following the procedure of Example 1.

Example 6.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (isoxazole - 5 - carbonyl) - piperazin - 1-yl]quinazoline Hydrochloride — A solution of isoxazole-5-carbonyl chloride (1.33 g., 0.01 mmole) in dioxane was added to a solution at 30°C. of 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline (2.94 g., 0.01 mole) in dioxane. The mixture was stirred at reflux for three minutes, then at room temperature for 16 hours. Filtration gave the title compound (4.02 g., 94% yield). Recrystallization from aqueous methanol gave a product having a m.p. of 270°C. with decomposition.

Anal. Calcd for $C_{18}H_{20}N_6O_4 \cdot HCl$: C, 51.37; H, 5.03; Cl, 8.42; N, 19.97
Found: C, 50.86; H, 4.65; Cl, 8.52; N, 19.81.
(corrected for 4.30% H_2O)

Example 7.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (isoxazole - 3 - carbonyl) - piperazin-1-yl]quinazoline Hydrochloride — A solution of isoxazole-3-carbonyl chloride (0.753 g., 0.0057 mole) in dioxane (20 ml.) was added to a solution of 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline (1.66 g., 0.0057 mole) in dioxane (60 ml.). The mixture was stirred at reflux for 30 minutes, then at room temperature for 64 hours. Filtration gave the title compound which was recrystallized from methanol (1.81 g., 75% yield). The product had a m.p. of 268—273°C. with decomposition.

Anal. Calcd for $C_{18}H_{20}N_6O_4 \cdot HCl$: C, 51.37; H, 5.03; Cl, 8.42; N, 19.97
Found: C, 50.04; H, 4.86; Cl, 8.66; N, 19.57
(corrected for 3.11% H_2O)

Example 8.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (isoxazole - 4 - carbonyl) - piperazin - 1-yl]quinazoline Hydrochloride — A solution of isoxazole-4-carbonyl chloride (1.06 g., 8.08 mmole) in dioxane (8 ml.) was added to a solution of 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline (2.34 g., 8.08 mmole) in dioxane (200 ml.). The mixture was stirred at room temperature for 20 hours. Filtration gave the title compound, which, after recrystallization from methanol, had a m.p. of 255—260°C. with decomposition.

Anal. Calcd. for $C_{18}H_{20}N_6O_4 \cdot HCl$: C, 51.37; H, 5.03; Cl, 8.42; N, 19.97
Found: C, 51.37; H, 4.95; Cl, 8.34; N, 19.95
(corrected for 1.63% H_2O)

Example 9.

4- Amino - 6,7 - dimethoxy - 2 - [4 - (5 - methylisoxazole - 3 - carbonyl)piperazin-1-yl]quinazoline Hydrochloride Hydrate — A solution of 5-methylisoxazole-3-

carbonyl chloride (0.41 g., 2.83 mmole) in dioxane was added to a solution of 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline (0.82 g., 2.83 mmole) in dioxane. The mixture was treated as described in the previous example to give the title compound having a m.p. of 271—273°C. with decomposition.

Anal. Calcd. for $C_{19}H_{22}N_6O_4HCl\ H_2O$: C, 50.38; H, 5.56; N, 18.56; H_2O 3.92
Found: C, 50.58; H, 5.40; N, 18.86; H_2O, 3.72

Example 10.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (3 - methylisoxazole - 4 - carbonyl)piperazin-1-yl]quinazoline Hydrochloride — A solution of 3-methyl-isoxazole-4-carbonyl chloride (1.01 g., 6.9 mmole) in dioxane and 4-amino-6,7-dimethoxy-2-(1-piperazinyl)-quinazoline (2.00 g., 6.9 mmole) in dioxane was stirred under reflux for 15 hours, then worked up as described in Example 6. The title compound after recrystallization from methanol had a m.p. of 300—301°C. with decomposition.

Anal. Calcd. for $C_{19}H_{22}N_6O_4HCl$: C, 52.47; H, 5.33; N, 19.33
Found: C, 52.62; H, 5.31; N, 19.12
(corrected for 1.13% H_2O)

Example 11.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (3 - methylisoxazole - 5 - carbonyl)-piperazin - 1 - yl]quinazoline Hydrochloride — A solution of 3 - methylisoxazole-5-carbonyl chloride (0.73 g., 5.02 mmole) in dioxane was added to a solution of 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline (1.45 g., 5.02 mmole) in dioxane. The mixture was heated briefly, then was stirred at 20°C. for 2.5 hours. Workup as in Example 6 gave the title compound having a m.p. of 263—264°C. with decomposition.

Anal. Calcd. for $C_{19}H_{22}N_6O_4HCl$: C, 52.47; H, 5.33; Cl, 8.15; N, 19.33
Found: C, 51.82; H, 5.04; Cl, 8.36; N, 19.46
(corrected for 4.82% H_2O)

Example 12.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (oxazole - 4 - carbonyl)piperazin - 1 - yl]-quinazoline Hydrochloride Hydrate — A solution of oxazole-4-carbonyl chloride (0.73 g., 5.53 mmole) in dioxane was added to a solution of 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline (1.60 g., 5.53 mmole) in dioxane. The mixture was heated at reflux for 0.5 hour, then was stirred at 20°C for 64 hours. Filtration gave the title compound having a m.p. of 291—294°C. with decomposition after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{18}H_{20}N_6O_4HCl\ .\ H_2O$: C, 49.26; H, 5.28; Cl, 8.08; N, 19.15
Found: C, 48.92; H, 4.83; Cl, 8.33; N, 18.94

Example 13.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (2 - methyloxazole - 4 - carbonyl)piperazin-1-yl]quinazoline Hydrochloride — A solution of 2-methyloxazole-4-carbonyl chloride (1.01 g., 6.9 mmole) in dioxane was added to a solution of 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline (2.00 g., 6.9 mmole) in dioxane. The mixture was heated at reflux for 2 hours. Filtration gave the title compound having a m.p. of 278—280°C. with decomposition after recrystallization from methanol.

Anal. Calcd. for $C_{19}H_{22}N_6O_4HCl$: C, 52.47; H, 5.33; N, 19.33
Found: C, 52.08; H, 5.43; N, 18.89
(corrected for moisture)

Example 14.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (4 - methyloxazole - 5 - carbonyl)piperazin-1-yl]quinazoline Hydrochloride — The title compound was prepared from 4-methyloxazole-5-carbonyl chloride (0.85 g.) and 4-amino-6,7-dimethyl-2-(1-piperazinyl)quinazoline (1.68 g.) following the procedure of Example 6. The product had a m.p. of 283.5—288°C. with decomposition.

Anal. Calcd. for $C_{19}H_{22}N_6O_4HCl$: C, 52.48; H, 5.33; Cl, 8.15; N, 19.33
Found: C, 52.19; H, 4.94; Cl, 8.13; N, 19.05
(corrected f r 1.59% H_2O)

Example 15.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (isothiazole - 4 - carbonyl)piperazin - 1-yl]quinazoline Hydrochloride — The title compound was prepared from isothiazole-4-carbonyl chloride (1.01 g.) and 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline (1.99 g.) following previously described procedures. The product had a m.p. of 286—287°C. with decomposition.

Anal. Calcd. for $C_{18}H_{20}N_6O_3S$. HCl: C, 49.48; H, 4.84; Cl, 8.11; N, 19.23; S, 7.34
Found: C, 49.20; H, 4.81; Cl, 8.19; N, 19.27; S, 7.23
(corrected for 0.93% H_2O)

Example 16.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (thiazole - 2 - carbonyl)piperazin - 1-yl]quinazoline Hydrochloride — The title compound was prepared from thiazole-2-carbonyl chloride (0.79 g.) and 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline (1.54 g.) following previously described procedures. The product had a m.p. of 273—276°C. with decomposition.

Anal. Calcd. for $C_{18}H_{20}N_6O_3S$. HCl: C, 49.48; H, 4.84; N, 19.23
Found: C, 48.68; H, 4.62; N, 18.87
(corrected for 4.19% H_2O)

Example 17.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (thiazole - 4 - carbonyl)piperazin - 1-yl]quinazoline Hydrochloride — The title compound was prepared from thiazole-4-carbonyl chloride (1.02 g.) and 4-amino-6,7-dimethoxy-2-(1-pjiperazinyl)quinazoline (2.00 g.) following previously described procedures. The product had a m.p. of 274—277°C. with decomposition.

Anal. Calcd. for $C_{18}H_{20}N_6O_3S$. HCl: C, 49.48; H, 4.84; N, 19.24
Found: C, 49.11; H, 4.69; N, 19.31
(corrected for 4.47% H_2O)

Example 18.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (2 - methylthiazole - 4 - carbonyl)piperazin-1-yl]quinazoline Hydrochloride — The title compound was prepared from 2-methylthiazole-4-carbonyl chloride (0.49 g.) and 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline (0.87 g.) following previously described procedures. The product had a m.p. of 260—263°C. with decomposition.

Anal. Calcd. for $C_{19}H_{22}N_6O_3S$. HCl: C, 50.60; H, 5.14; N, 18.64
Found: C, 50.88; H, 4.96; N, 18.67
(corrected for 2.88% H_2O)

Example 19.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (thiazole - 5 - carbonyl)piperazin - 1-yl]quinazoline Hydrochloride — The title compound was prepared from thiazole-5-carbonyl chloride (0.77 g.) and 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline (1.51 g.) folowing previously described procedures. The product had a m.p. of 280—281°C. with decomposition.

Anal. Calcd. for $C_{18}H_{20}N_6O_3S$. HCl: C, 49.48; H, 4.84; Cl, 8.11; N, 19.23; S, 7.34
Found: C, 49.22; H, 5.19; Cl, 8.31; N, 19.49; S, 6.79
(Corrected for 2.63% H_2O)

Example 20.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (2 - methylthiazole - 5 - carbonyl)piperazin-1-yl]quinazoline Hydrochloride — The title compound was prepared from 2-methylthiazole-5-carbonyl chloride (0.42 g.) and 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline (0.75 g.) following previously described procedures. The product had a m.p. of 294—297°C. with decomposition.

Anal. Calcd. for $C_{19}H_{22}N_6O_3S$. HCl: C, 50.60; H, 5.14; N, 18.64
Found: C, 50.60; H, 4.95; N, 18.50
(corrected for 1.96% H_2O)

Example 21.

4 - Amino - 6,7 - dimethoxy - 2 - [4 - (4 - methylthiazole - 5 - carbonyl)piperazin-1-yl]quinazoline Hydrochloride — The title compound was prepared from 4-methylthiazole-5-carbonyl chloride (1.1 g.) and 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline (2.0 g.) following previously described procedures. The product had a m.p. of 293—295°C. with decomposition.

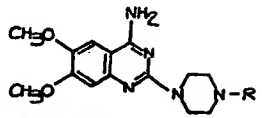
Anal. Calcd. for $C_{19}H_{22}N_6O_3S$. HCl: C, 50.60; H, 5.14; N, 18.64
Found: C, 50.47; H, 4.78; N, 18.43
(corrected for 4.72% H_2O)

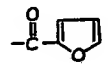
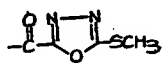
To determine the efficacy of the compounds of this invention as antihypertensive agents, tests were conducted comparing these products to prazosin.

Table 1 below sets forth the comparison of the product of Example 1 to prazosin. As shown in Table 1, the product obtained in Example 1, above (hereinafter referred to as BL—5111) is of comparable antihypertensive potency to prazosin, but has little or none of the peripheral α-adrenergic blocking properties shown by prazosin. This compound thus represents a significant and unexpected advance in the continuing quest for potent antihypertensive drugs which have little or no potential for side effects as reflected by their lack of α-adrenergic blocking activity.

In Table 1, antihypertensive activity was determined by oral administration to spontaneous hypertensive rats, and the *in vitro* and *in vivo* α-adrenergic receptor blocking effect was determined by tests described following Table 1. In the *in vitro* test, the inhibition by BL—5111 of norepinephrine induced contractions of rat seminal vesicles was measured; and in the *in vivo* test, the inhibition by BL—5111 of norepinephrine induced pressor responses in anesthetized dogs was measured. The *in vivo* tests were conducted using intravenous administration, each compound being assayed in 4 dogs with 2 dose response results in each dog.

TABLE 1



Compound	R	Antihypertensive Activity: Dose mg/kg	% Blood Pressure Change	ED50 mm Hg mg/kg	Activity Ratio	α-Adrenergic Receptor Blocking Effect: In Vitro Activity Ratio	In Vivo Activity Ratio	IV LD_{50} in mice mg/kg
Prazosin		10	-42	2.1	1.0	1.0	1.0	35.1
		3	-29					
		1	-14					
BL-5111		10	-41	2.3	0.91	0	0.04	45.7
		3	-26					
		1	-19					

ISOLATED RAT SEMINAL VESICLE ASSAY.

Dangan et al, *Int. J. Neuropharmacol.*, 4:219 (1965) have shown that the seminal vesicle of the rat is a tissue which is notably responsive to compounds which activate α-receptors but is relatively insensitive to compounds which activate β-receptors. Lietch et al, *Brit. J. Pharmacol.*, 9:236 (1954), have employed the isolated rat seminal vesicle in the comparative assay of α-receptor blocking drugs and the present studies were carried out using a modification of their procedure.

Male Long Evans rats weighing approximately 300 g. were sacrificed by a sharp blow on the head. Seminal vesicles were removed and transfered to a shallow dish containing modified Tyrode's solution. The vesicles were emptied of their contents by squeezing them gently with a pair of forceps. Silk thread (4—0) was attached to both ends of the vesicle and it was suspended in a 20 ml. muscle chamber containing modified oxygenated Tyrode's solution (g./liter: NaCl 8, KCl 0.2, $CaCl_2$ 0.26, $NaHCO_3$ 1, Na_2HPO_4 0.0575, glucose 0.5 and $MgCl_2$ 0.02). The bathing fluid was maintained at 37°C. with a thermostatically controlled isolated organ tissue bath. Contractions were recorded isometrically by means of a force displacement transducer and recordings were made with a Beckman RP Dynograph. ("Beckman" is a registered Trade Mark). Norepinephrine (NE) was added to the muscle chamber in volumes ranging from 0.1 to 0.4 ml. with a one ml. syringe attached to a 3 inch 20 gauge needle. NE and test compounds were dissolved in deionized water.

NE dose response curves were obtained alone and in the presence of test compounds. NE was allowed to remain in contact with the strip until a maximal contraction was obtained. The strip was then washed with the perfusion fluid for 15—30 seconds and the preparation was allowed to return to base line before a subsequent dose of NE was given. Increasing amounts of NE were injected into the bath in the same manner until a complete dose response was obtained.

The seminal vesicles used to obtain the control NE dose response were discarded and new preparations were placed in the tissue bath for evaluation of the test compound. The test compound was added directly to the perfusion fluid (10 nanograms/ml.) and the strips were allowed to remain in contact with the bathing media for at least 10 minutes before the NE dose response was determined.

ED50 values for NE were obtained by regression analysis as described by Finney, *Probit. Analysis*, 2d Ed., Cambridge (1964). A minimum of 4 strips and at least 4 doses were employed to calculate the regression lines. The ED50 value is defined as the concentration of NE which produces a contraction equal to 50% of the maximal contraction.

The ratio of the α-adrenergic blocking activity of BL—5111 relative to that of prazosin was calculated as follows:

$$\% \text{ Change from NE} = \frac{\text{ED50 NE + Drug} - \text{ED50 NE Alone}}{\text{ED50 NE Alone}} \times 100$$

The value obtained for BL—5111 was then expressed as a ratio of the value obtained for prazosin.

$$\text{Activity Ratio} = \frac{\% \text{ Chance for NE} - \text{BL—5111}}{\% \text{ Change from NE} - \text{prazosin}}$$

The results obtained with NE, prazosin and BL—5111 are summarized in Table II.

TABLE II

Effect of Prazosin and BL—5111 on NE Response in Isolated Rat Seminal Vesicles

Treatment	No. of Strips	NE ED50 with 95% Conf. Limits (μg/ml)	Percent Change From Control	Activity Ratio Relative to Prazosin
Control	32	0.89 (0.84—0.94)	—	—
Prazosin, 10 nano/ml.	8	6.03 (5.30—6.81)	578	1.0
BL—5111 10 nano/ml.	7	0.93 (0.80—1.08)	4.5	0.008

These data indicate rather clearly that at a concentration of 10 nanograms/ml., prazosin caused nearly a six fold decrease in the sensitivity of isolated rat seminal vesicles to the stimulant activity of NE while BL—5111 was essentially inactive in this respect. It was concluded that BL—5111 possesses less than one percent of the α-adrenergic blocking activity of prazosin.

ANESTHETIZED DOG ASSAY FOR α-ADRENERGIC BLOCKING AGENTS

Nash, C. B., *Pharmacological Research Communications*, 4:423, (1969) and Maxwell, R. A., *Drill's Pharmacology in Medicine*, (1971) p. 683 have shown that in anesthetized dogs α-adrenergic blocking agents antagonize the blood pressure elevating effects of intravenous norepinephrine. Thus, blood pressure responses to norepinephrine (NE) in anesthetized dogs was used as a comparative assay for α-adrenergic receptor blocking properties of drugs.

Experiments were done on mongrel dogs anesthetized with sodium pentobarbital, 30 mg./kg. iv. The left femoral artery was cannulated to record aortic blood pressure and a femoral vein was cannulated for administration of drugs. All animals underwent a bilateral vagotomy. A norepinephrine dose-response curve was obtained by administering increasing doses of iv. norepinephrine (0.01—1 μg/kg). The test drug (prazosin, BL—5111) was then administered iv. at 3 mg/kg. Approximately 30 minutes later a dose-response curve was again established for iv. norepinephrine (0.01—10 μg/kg). The dose of norepinephrine (with 95% confidence limits) that increased blood pressure by 50 mm of Hg was obtained from dose-response curve analysis before and after prazosin and BL—5111. The ratio of the α-adrenergic blocking activity of BL—5111 relative to that of prazosin was obtained as follows:

$$\text{Activity Ratio} = \frac{\text{ED50 mm Hg BL—5111} - \text{ED50 mm Hg NE}}{\text{ED50 mm Hg Prazosin} - \text{ED50 mm Hg NE}}$$

The results obtained with norepinephrine, prazosin and BL—5111 are summarized in Table III. The results indicate that BL—5111 was approximately 30 times less active than prazosin in causing α-adrenergic blockade at 3 mg/kg iv.

TABLE III

Effect of: Prazosin and BL–5111 on the Blood Pressure Response to Intravenous Norepinephrine

Treatment	N	NE ED50 mm Hg w/ 95% Conf. Limits	Activity Ratio Relative to Prazosin
Control	20	0.23 (0.19–0.28)	–
Prazosin, 3 mg/kg	4	6.90 (4.80–10.7)	1.000
BL–5111	4	0.47 (0.40–0.55)	0.036

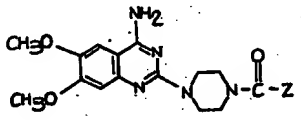
Table IV below sets forth the comparison test data for the products of Examples 6—21 and prazosin. As shown in this table, the products obtained in the foregoing Examples 6—21 are of comparable antihypertensive potency to prazosin, but have generally less of the peripheral α-adrenergic blocking properties shown by prazosin. These compounds thus represent a significant and unexpected advance in the continuing quest for potent antihypertensive drugs.

TABLE IV

Example	Antihypertensive Activity: Dos mg/kg	Antihypertensive Activity: % Blood Pressure Change	α-Adrenergic Receptor Blocking Effect: In Vitro Activity Ratio	α-Adrenergic Receptor Blocking Effect: In Viv Activity Ratio
Prazosin (Reference Drug)	10	-42	1.0	1.0
	3	-29		
	1	-14		
6	10	-35	0.11	0.18
	3	-26		
	1	-15		
7	10	-32		
	3	-26		
	1	-12		
8	10	-35	0.92	
	3	-23		
	1	-13		
9	10	-41	0	0.24
	3	-18		
	1	-14		
10	10	-33	0.30	0.18
	3	-29		
	1	-17		
11	10	-37	0.25	
	3	-21		
	1	-18		
12	10	-45	0.6	1.22
	3	-29		
	1	-15		
13	10	-35	0.17	
	3	-31		
	1	-13		
14	10	-41	0.19	
	3	-26		
	1	-14		
15	10	-25		
	3	-23		
	1	-14		
16	10	-33		
	3	-27		
	1	-14		
17	10	-32	0.12	
	3	-24		
	1	-20		
18	10	-28	0.02	
	3	-28		
	1	-19		
19	10	-33	0.10	
	3	-22		
	1	-12		
20	10	-37	0.19	0.09
	3	-25		
	1	-20		
21	10	-28	0.35	
	3	-22		
	1	-4		

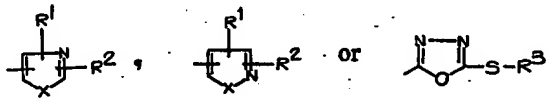
WHAT WE CLAIM IS:—

1. Compounds having the formula



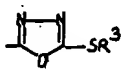
I

in which Z is



wherein X is either oxygen or sulfur, R^1 and R^2 may be the same or different and are selected from hydrogen, alkyl having from 1 to 6 carbon atoms, alkoxy having from 1 to 6 carbon atoms and alkylthio having from 1 to 6 carbon atoms, and R^3 is alkyl having from 1 to 6 carbon atoms; or pharmaceutically acceptable acid addition salts thereof.

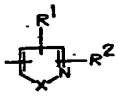
2. A compound of Claim 1, in which Z is the radical



and R^3 is alkyl of 1 to 4 carbon atoms or a pharmaceutically acceptable acid addition salt thereof.

3. A compound according to Claim 2, or a pharmaceutically acceptable acid addition salt thereof, wherein R^3 is methyl.

4. The compound of Claim 1, in which Z is the radical

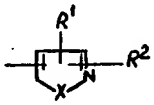


in which X, R^1 and R^2 are as defined in Claim 1.

5. A compound of Claim 4 in which X is oxygen.

6. A compound of Claim 4 in which X is sulfur.

7. A compound of Claim 1, in which Z is the radical



in which X, R^1 and R^2 are as defined in Claim 1.

8. A compound of Claim 7 in which X is oxygen.

9. A compound of Claim 7 in which X is sulfur.

10. 4 - Amino - 6,7 - dimethoxy - 2 - [4 - (oxazole - 4 - carbonyl)piperazin - 1-yl] - quinazoline hydrochloride, optionally as its monohydrate.

11. 4 - Amino - 6,7 - dimethoxy - 2 - [4 - (isothiazole - 4 - carbonyl)piperazin-1-yl]-quinazoline hydrochloride.

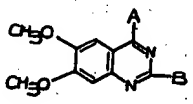
12. 4 - Amino - 6,7 - dimethoxy - 2 - [4 - (2 - methylthiazole - 4 - carbonyl)-piperazin - 1 - yl] - quinazoline hydrochloride.

13. 4 - Amino - 6,7 - dimethoxy - 2 - [4 - (2 - methylthiazole - 5 - carbonyl)-piperazin - 1 - yl] - quinazoline hydrochloride.

14. 4 - Amino - 6,7 - dimethoxy - 2 - [4 - (5 - methylisoxazole - 3 - carbonyl)-piperazin - 1 - yl] - quinazoline hydrochloride, optionally as its monohydrate.

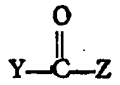
15. 4 - Amino - 6,7 - dimethoxy - 2 - [4 - (5 - methylthio - 1,3,4 - oxadiazole-2 - carbonyl) - piperazin - 1 - yl] - quinazoline hydrochloride.

16. A process for the preparation of a compound having the formula I as defined in Claim 1 or a pharmaceutically acceptable acid addition salt thereof; which process comprises reacting a quinazoline derivative of the formula



II

in which substituent A is $-NH_2$ or $-NR'_2$, wherein R'_2 is a conventional amine protecting group, and substituent B is chlorine, piperazino or OR'' wherein R'' is the radical $F_3CC(O)-$, CH_3SO_2-, F_3CSO_2-, or alkyl SO_2- with a reactant selected from



when B is piperazino and from

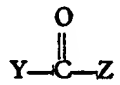
when B is other than piperazino, wherein Y is a carbonyl activating group of the type typically used in amidation reactions, and Z is as defined in Claim 1, when necessary, removing the amine protecting group R'_2 by conventional means and, if desired, converting the product to a pharmaceutically acceptable acid addition salt by methods known, *per se*.

17. The process of Claim 16, wherein

A is $-NH_2$ and

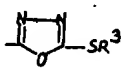
B is piperazino

in said compound of formula II and said reactant is



wherein Y and Z are as defined in Claim 16.

18. The process of Claim 17 wherein Z is



wherein R^3 is as defined in Claim 1.

19. The process of Claim 17 or 18 wherein said process is conducted in the presence of an inert solvent selected from dioxane, chloroform, methylene chloride and glycol dimethyl ether.

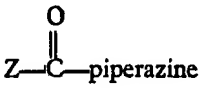
20. The process of Claim 19 wherein R^3 is methyl, Y is chlorine and the reaction is conducted in dioxane.

21. The process of Claim 16 wherein

A is $-NH_2$ and

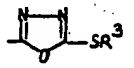
B is $-Cl$

in said compound of formula II and said reactant is



wherein Z is as defined in Claim 1.

22. The process of Claim 21 wherein Z is



wherein R^3 is as defined in Claim 1.

23. The process of Claim 22 wherein R^3 is methyl.

24. A pharmaceutical composition in dosage unit form adapted for administration to a mammal comprising a quinazoline compound according to any one of Claims 1 to 15 or a quinazoline compound prepared by the process of any one of Claims 16 to 23.

25. Quinazoline compounds according to Claim 1 substantially as hereinbefore described in the Examples.

26. A process for the preparation of quinazoline compounds according to Claim 1 substantially as hereinbefore described in any one of the Examples.

27. Quinazoline compounds whenever produced by the process of any one of Claims 16 to 23 or Claim 26.

28. A pharmaceutical composition comprising a compound in accordance with any one of Claims 1 to 15, Claim 25 or claim 27, or a pharmaceutically acceptable acid addition salt thereof, and an inert pharmaceutical diluent or carrier.

For the Applicants,
CARPMAELS & RANSFORD,
Chartered Patent Agents,
43 Bloomsbury Square,
London, WC1A 2RA.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1978.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.